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Opinion paper

# Outcome models in clinical studies: Implications for designing and evaluating trials in clinical nutrition

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SUMMARY

*Background & aims:* The selection of appropriate outcome variables in clinical nutrition is particularly challenging, since nutrition is an adjunct therapy in most cases. Therefore, its effect may be confounded with the primary therapy, and classic biomedical outcomes may not reflect the effect of the nutritional intervention. This paper scrutinizes different alternatives to the biomedical perspective.
*Results:* Five different outcome models are proposed and analyzed for their suitability in clinical nutrition studies: biomedical, patient-centered/-reported, health economic, decision-making, and integration of classical and patient-reported endpoints. Most published studies in the field of clinical nutrition make use of biomedical endpoints, but the growing importance of patient-centered/-reported and health economic outcomes is recognized. We recommend avoiding to focus solely on biomedical endpoints in clinical nutrition studies. The availability and value of a broader set of outcome-models should be acknowledged.
*Conclusion:* Patient-centered/-reported, health economic or combined endpoints are particularly useful to assess the effect of nutritional therapies, especially when applied in conjunction with a primary therapy. The proposed outcome models can also contribute to refine clinical nutrition guidelines in assessing the clinical relevance of the study results.


## 1. Introduction

Studies in clinical nutrition are difficult to design for a number of reasons:

1) In most instances nutritional inventions are adjunct therapies and their effects are confounded with the primary therapy. For example, in chemotherapy, tumor growth and tumor free survival are clearly useful endpoints. Such patients, however, may well profit in their quality of life and physical performance from nutritional therapies although this might not be reflected by the parameters above.
2) Stratification of patients is usually performed according to the degree of their primary disease rather than their nutritional and metabolic disorders. For example, intensive care unit patients with systemic inflammatory response syndrome (SIRS) are stratified according to APACHE scores rather than their degree of malnutrition.
3) Another difficulty in clinical nutritional studies is the designing of adequate control groups.[1] No general agreement exists on the definition of adequate controls for clinical nutrition studies. In many instances “placebo nutrition” is neither technically feasible nor ethically acceptable. Therefore, most studies compare different nutrition regimes instead of fasting vs. nutrition.

These general conditions make it particularly challenging to select an appropriate outcome model that is capable to capture the effect of a nutritional intervention.

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## 2. What is outcome?

The term "outcome" is not uniformly defined in the medical literature. "Outcome" usually refers to the effects of a therapy[2,3] and is thus used in the present article. The chosen outcome must perfectly match the research question, should be of importance for physicians and patients, and has to meet regulatory[4,5] and methodological[6,7] requirements. Outcome is operationalized via one or more endpoints. The most important endpoint is the primary endpoint and is the basis for sample size calculation. Other endpoints will become secondary endpoints. Researchers have to make clear whether their chosen endpoint is a true endpoint or surrogate endpoint. If true endpoints require long follow-up (e.g., five-year survival), surrogate endpoints that are detectable in a shorter period of time (e.g., time to progression) are often preferred. Criteria for choosing appropriate surrogate parameters have been described in the literature (e.g. Prentice criteria[6,8]). Another important consideration is the clinical relevance of differences.[7,9] In clinical nutrition, for instance, a difference in albumin plasma concentration of 0.2 g/L might be statistically significant, but is clinically not considered relevant.

### 2.1. Adjunct versus primary therapy

From a clinical perspective it may be of interest to distinguish between the effects of primary and adjunct therapies. In most cases, adjunct therapies are used in addition to a primary therapy to help reaching a common therapeutic goal. However, in some cases, adjunct therapies are initiated to reach very specific goals that are not within the scope of the primary therapy. Examples for such "specific" adjunct therapies are analgesia (goal: pain relief), physiotherapy (goal: maintaining mobility), or clinical nutrition. In clinical nutrition the classic goals are correction of metabolic derangements and improvements of nutritional status, but also physical functioning or quality of life. Whereas outcomes of primary therapies seem to be easily evaluated, the assessment of adjunct therapies is more difficult. In case of primary therapies, diagnostic criteria and outcome criteria are often identical, and the effect of the therapy is self-evident. Typical examples of outcomes of primary therapy would be normalization of body temperature in a patient with fever by antipyretic therapy or normalization of nutritional status in an undernourished patient by nutrition. In case of adjunct therapies, outcome evaluation is often more difficult, particularly because of the "noise of primary therapy". For example, if radio-chemotherapy improves swallowing in a patient with esophageal cancer, it may be difficult to separate this effect from the effect of concomitant nutritional therapy that facilitates swallowing by providing the patient with pureed food or liquid oral nutritional supplements.

### 2.2. Multimodal setting

Outcome definition and evaluation in a multimodal therapeutic setting is much more complicated, since the 1:1 relation between diagnostic and outcome criteria no longer exists; moreover, it is difficult to analyze the unique effects of each single therapeutic intervention. A good example is the Enhanced Recovery After Surgery (ERAS)-concept that includes several therapeutic measures including nutrition. A recent metaanalysis found that the inclusion of numerous ERAS elements resulted in a cumulative effect that is superior to traditional care.[10]

### 2.3. The five outcome models

Clinicians and researchers in the field of clinical nutrition have to face the diversity of outcome assessment and evaluation. Outcome may relate to somatic, psychological, or social aspects of health, functioning or well-being. These aspects can be evaluated from different perspectives, namely the patient, the physician, or the society. In an attempt to better structure outcome evaluation, five outcome models have been proposed.[2,3,11] Table 1 shows examples of endpoints for each outcome model that were consented by members of the German Society for Nutritional Medicine.

The respective values of these five models are discussed below.

## 3. Model 1: the biomedical model ("classical endpoints")

The biomedical model reflects a notion of health and disease that is defined via anatomical, physiological, or pathological concepts. All these aspects are assessed by physicians and observed by means of laboratory parameters or imaging procedures. Therefore, assessments obtained in the context of this model are considered objective and "hard" endpoints.

### 3.1. Survival

The "hardest" and most definite of all biomedical outcomes is survival. Conventionally, most clinical and epidemiological studies employ a 5-year observation period. For some conditions, such as intensive care therapy, shorter survival periods may be appropriate. Clinicians as well as authorities have required survival data as hard endpoints for the outcome evaluation of clinical nutrition. A typical example is the study by Griffiths et al., in which critically ill patients who received parenteral nutrition with glutamine supplementation showed longer survival rates than those without supplementation.[12]

However, numerous clinical nutrition studies failed to show effects on survival and other "hard" biomedical endpoints, but

**Table 1**
Examples of nutrition-specific or potentially nutrition-related endpoints in each outcome model.

| Model 1 biomedical endpoints | Model 2 patient-centered outcomes | Model 3 health economic parameters | Model 4 medical decision-making | Model 5 multi-component outcome models |
|---|---|---|---|---|
| Mortality (short-term/long-term) complications (e.g. infections, length of hospital stay, re-hospitalisation) disease progression<br>Wound healing<br>Time on ventilation<br>Weaning time<br>Therapy-related adverse reactions<br>Physical performance<br>Nutritional, inflammatory and/or immune status | Quality of life<br>Other patient-reported outcomes (PROs) such as<br>• Depression<br>• Pain<br>• Appetite assessment<br>• Activities of daily living (ADL)<br>• Patient satisfaction<br>• Hospital anxiety<br>• Coping | Use of health care resources<br>Costs for medication<br>Costs for complications<br>Length of hospital stay<br>Re-hospitalization<br>Personnel costs<br>Frequency of consultations<br>Time until occupational reintegration<br>Quality adjusted life years (QALYS)<br>Hospital vs. ambulatory care | Nutritional therapy vs. no nutritional therapy<br>Surgery vs. conservative therapy<br>Enteral vs. combined enteral and parenteral nutrition | Patient-generated Subjective Global Assessment (PG-SGA)<br>Crohn's disease activity index (CDAI)<br>Frailty Index |